REMARKS

Claims 1-15, 17-27, 29, 30 and 31 are pending in the present application. Claims 1-13, 21 and 22 have been withdrawn from consideration based on a restriction requirement. Claims 14, 15, 17-20, 23-27, 29, 30 and 31 are currently under examination.

Claims 14, 17, 18, 19, 20, 24, 25 and 27 have been amended herein. The specifics of those amendments are discussed below. Claim 31 has been added. No new matter has been added.

By way of review, the present invention provides a quick and effective method for assessing in a patient whether there has been axonal damage resulting from a traumatic CNS injury, and the extent of that damage. Until now, there is no effective, minimally invasive procedure for quickly determining that information which, of course, can be critical in an emergency room setting. In this method, a patient suspected of having such traumatic CNS injury, such as primary neuronal injuries, primary hemorrhages, primary vascular injuries, or secondary traumatic lesions, provides a sample of cerebrospinal fluid. The presence in that fluid of specific tau proteins or fragments of those proteins are then determined using a monoclonal antibody raised against those proteins.

In paragraph 6 of the Office Action, the Examiner rejected Claims 14-15, 17-20, 23-27 and 29-30, under 35 USC §112, first paragraph, contending that use of the phrase "derivatives thereof" in those claims constitutes new matter. Claims 14, 17, 19, 24, 25 and 27 have been amended so as to eliminate the phrase "derivatives thereof". In light of that amendment, it is respectfully submitted that this rejection is moot and should be withdrawn.

In paragraph 7 of the Office Action, the Examiner has rejected Claims 14-15, 17-20, 23-27 and 29-30, under the first paragraph of 35 USC §112, contending that the disclosure is not enabling for derivatives and fragments of the disclosed proteins. As discussed above, the phrase "derivatives thereof" has now been eliminated from the claims, thereby rendered that portion of the rejection moot. Tau protein fragments are disclosed in the present application (for example, at page 5, lines 5-22; page 16, line 20 through page 17, line 7; page 18, lines 12-19, and in Figure 4). Based on this disclosure, and the disclosure of the tau protein itself, one skilled in the art would understand what was meant by "fragments" of the disclosed tau protein and would be able to raise an antibody to those fragments. Accordingly, based on the disclosure of the present application, it is respectfully submitted that this portion of the rejection should be withdrawn. In any event, newly-added Claim 31 is identical to Claim 14, except that it does not include the "fragments thereof" language. Claim 31, therefore, should not be subject to this rejection made by the Examiner.

In paragraph 8 of the Office Action, the Examiner has rejected Claims 19-20, under the second paragraph of 35 USC §112, stating that the phrase "derivatives thereof" does not define materials of a specific reference sequence. As discussed above, the phrase "derivatives thereof" has been eliminated from Claims 19 and 20, thereby rendering this rejection moot.

In paragraph 9 of the Office Action, the Examiner has rejected Claims 17-20, under the second paragraph of 35 USC §112, contending that there is no antecedent basis for the phrase "at least one isoform of tau protein" used in those claims. Claims 17, 18, 19 and 20 have been amended so as to insert the language suggested by the Examiner in the

Office Action. In light of these amendments, it is respectfully submitted that this rejection has been overcome and it is requested that it be withdrawn.

The obvious typographical error in the sequence listing pointed out by the Examiner has also been corrected, with a corrected disc enclosed.

Finally, in paragraph 10 of the Office Action, the Examiner has rejected Claims 14-15, 17-20, 23-27 and 29-30, under 35 USC §102(b), as being anticipated by WO 94/13795 (hereinafter "Vandermeeren, et al."). As described above, the present invention relates to a method for assessing the presence and degree of traumatic CNS injury in a patient. Accordingly, Claim 14 has been amended (antecedent basis at page 4, line 17 through page 5, line 4) to better define the specific types of traumatic injury which the present assay is used to detect. Specifically, Claim 14 is drawn to use with a patient suspected of having primary neuronal injuries, primary hemorrhages, primary vascular injuries, dural sinus laceration or occlusion, traumatic pia-arachnoid injuries, cranial nerve injuries or secondary traumatic lesions.

The Vandermeeren, et al. patent, on the other hand, describes a group of monoclonal antibodies which can be used to detect tau protein in brain extracts and unconcentrated cerebrospinal fluid. These antibodies are taught to be useful for detecting the presence of Alzheimer's Disease and, secondarily, Down Syndrome, Pick's Disease and SSPE (see page 6, lines 6-9 and page 9, lines 23-27 of Vandermeeren, et al.). These diseases are known to be tied into the abnormal presence of tau protein. For example, in the case of Alzheimer's Disease, the disease is characterized by the presence of tau protein-containing neurofibrillary tangles (see page 6 of Vandermeeren, et al.). There is absolutely no suggestion in Vandermeeren, et al. to use the disclosed monoclonals for the

detection of traumatic CNS injury. Further, there is no suggestion that tau protein would be present in the cerebrospinal fluid of a patient with traumatic CNS injury or that the use of antibodies to tau protein could provide a quick and effective assay for traumatic CNS injury. Accordingly, the Vandermeeren, et al. reference does not disclose or suggest the use of the tau monoclonal antibodies with a patient suspected of having traumatic CNS injury, as the claims of the present application are now limited. Accordingly, rejection under 35 USC §102(b) and 103 is no longer applicable and it is respectfully requested that it be withdrawn.

In light of the foregoing, it is respectfully submitted that the rejections made by the Examiner in the August 16, 2000 Office Action have been overcome and it is requested that they be withdrawn. Accordingly, reconsideration and allowance of the claims of the present application, as amended herein, are earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to The Assistant Commissioner for Patents, Washington, D.C., 20231, this 8th day of May, 2001.

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Rachel Woods

CINlibrary/1053198.1

MARKED VERSION OF AMENDED CLAIMS

14. A method of determining axonal damage in the central nervous system **of a patient suspected of having a condition selected from primary neuronal injuries, primary hemorrhages, primary vascular injuries, dural sinus laceration or occlusion, traumatic pia-arachnoid injuries, cranial nerve injuries, and secondary traumatic lesions,** said method comprising the steps:

(a) obtaining a sample of cerebrospinal fluid from said [human patient central nervous system];

(b) treating said sample of cerebrospinal fluid with at least one monoclonal antibody, said at least one monoclonal antibody having been raised against an axonally-derived protein selected from the group consisting of isoforms of tau protein of SEQ ID NO: 1 ~~and derivatives~~ and fragments thereof; and

(c) detecting the presence of said axonally-derived protein bound to said at least one monoclonal antibody.

17. A method according to claim 16 wherein said **axonally-derived protein is a fragment** ~~at least one isoform~~ of said tau protein of SEQ ID NO: 1 ~~is a fragment of said tau protein~~ demonstrating an apparent molecular weight less than 50 kDa.

18. A method according to claim 17 wherein said **axonally-derived protein** ~~at least one tau protein fragment~~ demonstrates ~~ing~~ an apparent molecular weight in the range of about 30 kDa to about 50 kDa.

19. A method according to claim 18 wherein said **axonally-derived protein** ~~at least one tau protein fragment~~ comprises the sequence from serine^{199} to serine^{396} of tau protein **of SEQ ID NO: 1** ~~or derivatives thereof~~.

20. A method according to claim 19 wherein said **axonally-derived** ~~at least one tau protein fragment~~ tau protein lacks the native N-terminal and C-terminal amino acids

24. A method according to claim 23 wherein said axonally-derived protein bound to said at least one monoclonal antibody is a fragment of tau protein **of SEQ ID NO: 1** which is detected through gel electrophoresis and which gives rise to an electrophoresis gel demonstrating multiple protein bands with apparent molecular weights less than 50 kDa.

25. A method according to claim 24 wherein said axonally-derived protein bound to said at least one monoclonal antibody is a fragment of tau protein **of SEQ ID NO: 1** which is detected through gel electrophoresis and which gives rise to an electrophoresis gel demonstrating multiple protein bands with apparent molecular weights of from about 30 to 50 kDa.